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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/328,975	06/09/99	WOLFF J	MIRUS009

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EXAMINER
SCHNIZER,R

ART UNIT	PAPER NUMBER
1632	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/328,975	WOLFF ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10 and 12-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

An amendment and declaration were received and entered as Paper No. 8 on 2/8/01. Claims 9 and 11 were canceled as requested. Claims 1-8, 10, and 12-18 remain pending and are under consideration in this Office Action.

Rejections Withdrawn

The rejection of claim 8 under 35 USC 102 is withdrawn in view of Applicant's amendment, and in favor of new grounds of rejections.

The rejection of claims 8, 10 and 15 under 35 USC 103 is withdrawn in favor of new grounds of rejection.

Claim Rejections - 35 USC § 112

Claims 1-7 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for delivering to a cell *in vitro* a complex comprising a nucleic acid, a polymer and a charged polymer, does not reasonably provide enablement for the delivery of complexes *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for the reasons of record in Paper No. 7.

Claims 1-7 are directed to processes for delivering a nucleic acid to a cell *in vitro* or *in vivo*. See page 14, lines 10-12. The delivery of nucleic acids to cells *in vitro* has readily apparent

uses such as the expression and subsequent purification of desirable polypeptides. The specification teaches working examples of the use of the invention for delivery of nucleic acids to cells *in vitro*, and is fully enabled for this use.

The specification provides a single working example of the delivery of nucleic acids *in vivo*, in which a reporter gene is delivered and expressed. The specification fails to positively assert any utility for the delivery of nucleic acids *in vivo*, but the use of the invention for gene therapy is contemplated. See page 14, lines 14-19.

The state of the art of gene therapy was set forth in Paper No. 7. To summarize, the art of gene therapy is highly unpredictable, and success cannot be routinely obtained by those of skill in the art. Two problems associated with gene therapy are gene delivery and gene expression. The instant invention addresses problems with gene delivery, but fails to address gene expression difficulties. The specification fails to identify any specific gene which could be used to treat any specific disease, and provides no guidance as to dosages or administration profiles required to treat any disease. In addition, the results provided in Table 1 on page 27, and in the declaration of Dr. Trubetskoy, filed 2/8/01, do not provide convincing evidence that the instant invention improves DNA delivery relative to existing methods. As stated in Paper No. 7, Table 1 lacks any comparison to any known technique employed in gene therapy, the sample size is small (13 animals), and there is no control experiment or statistical analysis of the results. The declaration of Dr. Trubetskoy also fails to compare the results obtained to those obtainable by other known techniques. The demonstration of transfer and expression of genetic material to animals *in vivo* is

well established in the art, as is the inability to routinely use this technique for therapeuitic purposes. For these reasons, one of skill in the art could not conclude that the instant invention could be used to practice gene therapy with a reasonable expectation of success.

Because those of skill in the art cannot currently practice gene therapy with routine success, and because the instant application fails to provide the guidance which is missing from the prior art, one of skill in the art could not use the claimed invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments filed 2/8/01 have been fully considered but they are not persuasive.

Applicant argues that the claimed process may be used in gene therapy development and relies for support on page 1, lines 18-20 of the specification. This passage states that "[p]olymers have been used in research for the delivery of nucleic acids... to cells with the eventual goal of providing therapeutic processes." Thus Applicant contends that the invention has a readily apparent use as an intermediate step in the process of developing a final product, which product would be a successful gene therapy protocol.

In response, the examiner asserts that the intermediate steps in a non-enabled process lack enablement themselves if they have no other enabled use. Applicant must teach how to use the claimed invention. This obligation cannot be shifted to those who would use the instant invention to find some patentable purpose for it. Applicant argues that it would be improper to suggest that

only the final product in the development of a process may be patented, but cites no support for this argument. Because the specification fails to teach any enabled *in vivo* use for the claimed products and processes, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 10, and 12-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 and 15-18 are indefinite because they recite "the complex having a net charge" without antecedent basis.

Claims 10, 12, and 14 are indefinite because they depend from canceled claims.

Claim 13 is indefinite because it recites "the charged polymer" without antecedent basis.

Claim 16 is indefinite because it recites "the polycation" without antecedent basis.

Claims 17 and 18 are indefinite because they recite "the negatively charged polyion" without antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8, 10, 15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Boussif et al (Proc. Nat. Acad. Sci. 92:7997-7301, 8/1995).

Boussif teaches a method of making nucleic acid/PEI complexes, and their use in transfecting mammalian cells *in vivo*. See abstract, and paragraph bridging columns 1 and 2 on page 7298. Boussif teaches that complex formation should take place in a stepwise fashion in which a solution of PEI is added dropwise to a solution of nucleic acid. See sentence bridging columns 1 and 2 on page 7299. Boussif also teaches that polymer counterion condensation is a cooperative process, implying that binding interactions increase with the addition of each drop of PEI to the DNA solution. See column 2 on page 7299, lines 4 and 5. For this reason, addition of a first drop of PEI to a nucleic acid solution will result in the formation of complexes having a net charge, and addition of further drops will result in additional binding, and modification of the net charge of these complexes. Thus Boussif anticipates the claims.

Claims 8, 10, and 13 are rejected under 35 U.S.C. 102(e) as being anticipated by Kabanov et al (US Patent 5,656,611, issued 8/12/97).

Kabanov teaches a complex comprising nucleic acids complexed with a polycationic block copolymer. See column 3, lines 1-37, especially lines 1 and 34-37. The nucleic acid can be considered to act as the polyanion polymer, thus Kabanov anticipates the claims. For the purpose of examination under 35 U.S.C. 102, claim 10 has been considered to be dependent on claim 8.

Claims 8, 10, 15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Baker et al (Nucl. Acids Res. 25(10): 1950-1956, 5/1997), as evidenced by Boussif.

Baker teaches compositions comprising nucleic acids complexed with either polylysine/adenovirus conjugates or polyethyleneimine/adenovirus conjugates, and their use in transfecting mammalian cells. The nucleic acid can be considered to act as the polyanion polymer recited by claims 8 and 10. For the purpose of examination under 35 U.S.C. 102, claim 10 has been considered to be dependent on claim 8. Claims 15 and 16 are included in the rejection for the following reasons. Baker teaches that increasing amounts of PEI/adenovirus conjugate result in increased transfection efficiency, implying that more than one PEI/adenovirus conjugate binds to each nucleic acid. See Fig. 3 on page 1954. It is well known in the art that DNA/polycation condensation is a cooperative process (see Boussif, above) thus the binding interaction between DNA and polycations is a multi-step event wherein a single binding interaction influences further binding interactions. Thus, an initial nucleic acid/PEI complex will have a certain net charge, and

will promote the binding of more nucleic acids or PEI molecules which will subsequently change the net charge of the initial complex. Thus Baker anticipates the claims.

Response to Arguments

Applicant's arguments filed 2/8/01 have been fully considered as they might apply to both the original and new grounds of rejection, but they are unpersuasive.

Applicant argues that "[c]laim 8 has been amended to recite attaching a charged polymer to change the net charge." This is incorrect. Amended claim 8 fails to recite the attachment of any charged polymer or the change of any net charge. Nonetheless, the rejection of claims 8 and 10 under 35 USC 103 has been withdrawn because the amended claims are now anticipated by a single one of the reference cited in the obviousness rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 103-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Patsy Zimmerman whose telephone number is 703-308-8338.

Richard Schnizer, Ph.D.

Karen M. Hauda

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